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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,195	11/14/2003	Joffre B. Baker	GHDX-005	5745

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EXAMINER	
SHAW, AMANDA MARIE	

ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
12/12/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/714,195	BAKER ET AL.	
	Examiner	Art Unit	
	AMANDA SHAW	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31,35-38,40-47,51,52,59,60,62 and 64* is/are pending in the application.

4a) Of the above claim(s) *40 and 64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31,35-38,41-47,51,52,59,60 and ,62* is/are rejected.

7)☒ Claim(s) *60* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed October 17, 2008. This action is made FINAL.

Claims 31, 35-38, 40-47, 51-52, 59-60, 62, and 64 are currently pending. Claims 31, 38, 60, and 62 have been amended. Claims 40 and 64 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim.

Further it is noted for the record that the Office Action dated July 18, 2008 was non final. The examiner regrets the confusion.

Withdrawn Objections

2. The objections to claims 56, 62, and 63 made in section 5 of the Office Action of July 18, 2008 are moot in view of the cancellation of claims 56 and 63 and in view of the amendment made to claim 62.

Withdrawn Rejections

3. The rejection made under 35 USC 112 2nd paragraph in section 6 of the Office Action of July 18, 2008 is withdrawn in view of the amendments made to the claims.

The rejection made under 35 USC 102(b) in section 9 of the Office Action of July 18, 2008 is withdrawn in view of the amendments made to the claims.

The rejections made under 35 USC 103(a) in sections 11-15 of the Office Action of July 18, 2008 are withdrawn in view of amendments made to the claims.

Claim Objections

4. Claims 60 is objected to because the claim recites RNA transcripts which have not been elected.

Claim Rejections - 35 USC § 112 1st paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31, 35-38, 41-47, 51-52, 59-60, and 62 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance

presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Nature of the Invention

Claim 31 is drawn to a method for predicting the likelihood that a human colon cancer patient will exhibit a clinically beneficial patient response to treatment with an ErbB1 inhibitor. Claim 31 comprises (i) assaying a normalized level of LAMC2 in a sample comprising ErbB1 expressing colon cancer cells obtained from said patient; (ii) analyzing the normalized level of the LAMC2 transcript; and (iii) predicting the likelihood of response of the patient to treatment with an ErbB1 inhibitor based on the normalized level of the LAMC2 transcript, wherein the normalized level of LAMC2 RNA transcript correlates with clinically beneficial patient response to treatment with an ErbB1 inhibitor, wherein the ErbB1 inhibitor is erlotinib, cetuximab, or gefitinib. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)). The nature of the invention requires the knowledge of a reliable association between the level of LAMC2 in a sample and how a patient will respond to treatment with an ErbB1 inhibitor, specifically erlotinib, cetuximab, or gefitinib.

Scope of the Claims:

In the instant case the claims are extremely broad for several reasons. Independent claim 31 is broadly drawn to method for predicting the likelihood that a human colon cancer patient will exhibit a clinically beneficial patient response to treatment with erlotinib, cetuximab, or gefitinib based on the level of LAMC2 in a

patients sample. The claims require a step of "predicting the likelihood of response of the patient to treatment with an ErbB1 inhibitor based on the normalized level of the LAMC2 transcript". This step is problematic because the claim does not recite how one would use the LAMC2 level to make the prediction. For example is the prediction that a patient will exhibit a clinically beneficial response made when LAMC2 is over expressed or under expressed? Dependent claim 60 is also broad because it is drawn to a method further comprising determining the normalized level of CD44v6 wherein an increased normalized level of CD44v6 indicates that the patient will show a decreased likelihood of response to treatment with ANY ErbB1 inhibitor.

Teachings in the Specification and Examples:

The specification (page 25) teaches that EGFR (also known as ErbB1) is known to be active in several tumor types such as breast, colon, and head and neck cancers. The specification also teaches that several EGFR inhibitors are promising drug candidates for the treatment of EGFR expressing cancers. The specification further teaches the following EGFR inhibitors: (i) Iressa (gefitinib) is a small synthetic quinazoline that competitively inhibits the ATP binding site of EGFR and has been in Phase III clinical trials for the treatment of non-small-cell lung carcinoma; (ii) [agr]cyano-[bgr]methyl-N-[(trifluoromethoxy)phenyl]-propenamide (LFM-A12) has been shown to inhibit the proliferation and invasiveness of EGFR positive human breast cancer cells; (iii) Cetuximab is a monoclonal antibody that blocks the EGFR and EGFR -dependent cell growth that is currently being tested in phase III clinical trials; and (iv) Tarceva™

(erlotinib) which has shown promising indications of anti-cancer activity in patients with advanced ovarian cancer, and non-small cell lung and head and neck carcinomas.

The specification teaches (Example 2) that twenty-three colon adeoncarcinoma patients in all were studied using a 192-gene assay. Following treatment with an unspecified EGFR inhibitor, three patients were determined to have had a partial response, five to have stable disease, and fifteen to have progressive disease. Table 3 shows the results obtained using the partial response criterion. LAMC2 was found to be over expressed. Specifically LAMC2 had a negative response and a p value of 0.0357. Here the term "negative" indicates that greater expression of the gene decreased likelihood of response to treatment with EGFR inhibitor, and "positive" indicates that increased expression of the gene increased likelihood of response to EGFR inhibitor (page 28). Table 4 shows the results analysis of colon cancer patient data using clinical benefit criteria. Here there is no data provided for LAMC2. Further with respect to claim 60 Table 4 shows that CD44v6 had a negative response and a p value of 0.0047.

In the instant case the specification does not teach which ErbB1 inhibitors were used. However it is noted for the record that the Applicants have submitted a declaration by Joffre B. Baker, PhD stating that the patients were treated with an ErbB1 inhibitor selected from erlotinib, gefitinib, cetuximab, EMD72000, and AEE788. Dr. Baker states that the results presented in tables 3 and 4 were the result of treatment with these EGFR inhibitors. However the tables do not show specific data for each individual inhibitor. For example there is no specific data that shows that patients with higher levels of LAMC2 have a decreased response to treatment with erlotinib or

that patients with higher levels of LAMC2 have a decreased response to treatment with cetuximab. Further only

Further it is noted that the specification only teaches an association between increased levels of LAMC2 and the response to treatment, yet the claims encompass a method of detecting both increased and decreased levels of LAMC2 and making a prediction based on these levels.

State of the Art and the Unpredictability of the Art:

The unpredictability of correlating a gene expression level with an individual's response to treatment is taught in the post filing date art by Evans (Nature 2004). Evans teaches that differences in DNA sequences that alter the expression or function of proteins that are targeted by drugs can contribute significantly to variation in the responses of individuals (Abstract). Evans teaches that most drug effects and treatment outcomes are determined by an interplay of multiple genes (Page 464 Column 2). Evans further teaches that although single gene defects can have a strong effect on their substrates, most of the phenotypic variability in drug response remains unexplained despite numerous efforts to interrogate candidate genes and pathways (Page 465, Column 1). Additionally Lee (The Oncologist 2005) teaches that while genes likely contribute to the observed variability in cancer treatment outcome, there are several other variables that have been found to be associated with drug responses such as age, gender, diet, drug-drug interactions (Abstract).

Further the art of determining if erlotinib, cetuximab, and gefitinib will be less effective in patients with increased LAMC2 levels is highly unpredictable. The post filing

date art of Giaccone teach six EGFR inhibitors (Iressa (gefitinib), Tarceva (erlotinib), lapatinib, cenertinib, ZD6474, and AEE788). Giaccone additionally teaches that each of these drugs has a different mechanism in which it acts on EGFR receptor. For example Iressa (gefitinib) and Tarceva (erlotinib) inhibit the tyrosine kinase of EGFR by competing with ATP for the ATP binding site, lapatinib and canertinib have activity on more members of the ErbB family, and ZD6474 and AEE788 inhibit the vascular endothelial factor receptor in addition to EGFR. Thus it is unpredictable as to whether the results obtained for colon cancer using whichever EGFR inhibitor the inventor used could be extrapolated to other EGFR inhibitors because each inhibitor works by a different mechanism.

Quantity of Experimentation:

The specification asserts that patients diagnosed with colon cancer with elevated levels of LAMC2 are less likely to respond to a treatment with an ErbB1 inhibitor. However the specification is silent as to which ErbB1 inhibitor was used. Therefore it is unclear if the claimed method would work for any ErbB1 inhibitor, specifically erlotinib, cetuximab, or gefitinib. Thus further experimentation would be required. For example, such experimentation may involve treating colon cancer patients with different types of ErbB1 inhibitors, namely erlotinib, cetuximab, or gefitinib and conducting multiple gene expression assays to determine the expression levels of LAMC2. Further these patients would have to be monitored to determine disease progression. Such random, trial by error experimentation is considered to be undue. The specification has provided only an invitation to experiment.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

The claims are drawn to a method for predicting the likelihood that colon cancer patients will respond to treatment with erlotinib, cetuximab, or gefitinib by determining the normalized level of LAMC2. As discussed above, whether an association exists between increased levels of LAMC2 and the response to each of these drugs is highly unpredictably. Further with regard to claim 60 the specification does not teach that increased expression of CD44v6 is associated with ANY ErbB1 inhibitor. Accordingly, although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the claimed invention.

Response to Arguments

6. Regarding the objection made to claim 60 the Applicants cite MPEP 803.04 for the teaching that in most cases, up to ten independent and distinct nucleotide sequences will be examined in a single application without restriction. This argument has been fully considered but is not persuasive because the USPTO has published a pre-OG notice regarding its new position on restriction practice in pending applications that relate to nucleic acid sequences. Prior to this notice, the PTO had been officially operating under the direction of an Official Gazette notice dated November 19, 1996. The old notice allowed for a partial waiver of requirements for restriction and unity of invention for applications relating to nucleotide sequences by permitting examination of a "reasonable" number -- typically up to ten -- independent and distinct molecules described by their nucleotide sequences in a single patent application. This newly published notice effectively rescinds the 1996 notice, and requires that claims to polynucleotide sequences "be considered for independence, relatedness, distinction and burden as for claims to any other type of molecule." In the instant application each gene constitutes an independent and distinct invention within the meaning of 35 USC 121 since each gene consists of a different nucleotide sequence, has a different melting point, a different specificity of hybridization and encodes for a protein having a different biological activity. Therefore, a search for multiple genes or multiple combinations of genes is an undue burden on the office. As such the restriction to one RNA transcript for claim 60 was proper. Until claim 31 is found allowable, claim 60 will be objected to for

reciting non elected RNA transcripts. Additionally it is noted for the record that if claim 31 is found allowable it does not necessarily mean that claim 60 will be allowable because the examiner will first have to consider if the specification provides enablement for each of the additional genes recited by claim 60.

Regarding the enablement rejection the Applicants argue that claim 31 currently recites that the ErbB1 inhibitor interacts with an ErbB1 receptor. They further state that those skilled in the art as of November 15, 2002 were aware of a number of ErbB1 inhibitors that interact with an ErbB1 receptor. Then Applicants refer to the declaration filed by Joffre B. Baker, PhD stating that the patients in example 2 were treated with an ErbB1 inhibitor selected from erlotinib, gefitinib, cetuximab, EMD72000, and AEE788 and that the results presented in tables 3 and 4 were the result of treatment with these EGFR inhibitors. Therefore since they have shown a negative correlation between LAMC2 levels and patient response to at least 3 classes of ErbB1 inhibitors (i.e. quinazoline class, monoclonal antibody class, and pyrrolopyrimidine class) they believe the claims are enabled for ErbB1 inhibitors in these classes, and specifically erlotinib, cetuximab, or gefitinib. This argument has been fully considered but is not persuasive. In the instant case the data present in Tables 3 and 4 reflects the response to treatment with 5 different ErbB1 inhibitors; however the Applicants have not provided data for each individual drug being claimed (erlotinib, cetuximab, or gefitinib). That is, the declaration and specification as originally filed do not provide data which separately establish the levels of LAMC2 mRNA in subjects showing a beneficial response to erlotinib, subjects showing a beneficial response to cetuximab and subjects showing a

beneficial response to gefitinib. In the absence of a clear showing of an association between increased LAMC2 mRNA levels and a clinically beneficial response to each of the drugs erlotinib, cetuximab, or gefitinib, it remains unpredictable as to whether LAMC2 mRNA levels can be used to predict the likelihood of a beneficial response to these drugs.

Additionally the Applicants argue that they have provided ample guidance in the specification that indicates that there is an inverse correlation between response of a patient to treatment with an ErbB1 inhibitor and LAMC2 transcript levels. This argument has been fully considered but is not persuasive because although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). This portion of the enablement rejection could be overcome by reciting how the level of LAMC2 mRNA allows one to predict the likelihood that a human colon cancer patient will exhibit a clinically beneficial patient response. For these reasons the enablement rejection is maintained.

Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634

/Carla Myers/
Primary Examiner, Art Unit 1634